GUIDELINES

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Chinese guideline for the diagnosis and treatment of juvenile-onset recurrent respiratory papillomatosis (2024)

Working Group of Chinese Guideline for the Diagnosis and Treatment of JORRP | Subspecialty Group of Pediatrics, Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association | Editorial Board of *Chinese Journal of Otorhinolaryngology Head and Neck Surgery*

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ABSTRACT

The incidence of juvenile-onset recurrent respiratory papillomatosis (JORRP) varies worldwide, and the lack of well-adopted guidelines for use in China suggests that patients with JORRP do not receive optimal care. In America, where data is available, pediatric patients undergo an average of 4 surgeries annually and a total of >40 surgeries in their lifetimes primarily due to this condition. It is widely accepted that timely diagnosis and implementation of scientifically sound and effective interventions can prevent JORRP progression and mitigate serious complications. Notably, evidence-based guidelines to coordinate care are lacking, and there is a need to standardize clinical practice to improve outcomes for patients.

The International Pediatric Otolaryngology Group (IPOG) issued guidelines in 2020 to improve care for patients with JORRP. However, this guideline was majorly tailored to the healthcare system in Europe and America, posing a challenge to its adoption in China. To this effect, we assembled a guideline development working group to formulate guidelines for the diagnosis and treatment of JORRP tailored to the Chinese context. The working group consisting of multidisciplinary experts with experience in managing patients with JORRP undertook qualitative and quantitative studies, conducted two rounds of Delphi consensus, and carried out multiple systematic reviews/meta-analyses to provide 24 key recommendations to 12 questions of clinical interest.

We anticipate that healthcare workers, including primary care physicians and specialists managing JORRP, will find the guidelines useful, and their utilization will translate to improved outcomes for patients with the disease.

KEYWORDS

Consensus, Guidelines, Juvenile-onset recurrent respiratory papillomatosis, Management

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INTRODUCTION

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is the most common benign proliferative disease of the respiratory epithelium in children, caused by chronic infection with the low-risk human papillomavirus (HPV) 6/11.[1] Typically, JORRP manifests first between ages 2 and 3,[2, 3] with a roughly equal distribution between males and females. Incidence rates of JORRP vary significantly across countries, with a rate of 4.3 per 100 000 person-years[4] or 80–1500 cases annually[5] in the United States, 1.38 per 100 000 in South Africa,[6] 0.17 per 100 000 in Europe,[7] and no definitive reports from China. Unlike adult-onset recurrent respiratory papillomatosis (AORRP), JORRP is self-limiting with age and carries no risk of progressing to cancer; however, it has a higher recurrence rate.[2] Recent statistics show that children with laryngeal papilloma in the United States undergo an average of 4.4 surgeries per year, cumulating up to 40 surgeries in their lifetime.[8] In addition, the invasive nature of the disease may facilitate its spread to the lower respiratory tract and even to the lungs, leading to death. Timely diagnosis and implementation of scientifically sound and effective interventions can prevent disease progression and avoid serious complications.

Numerous controversies and challenges surround the diagnosis and treatment of JORRP in China. There is limited understanding of this condition among primary care doctors and hospitals in different regions, and the lack of standardized treatment protocols among hospitals further hinders progress in the diagnosis and treatment of JORRP in China. Currently, local and international guidelines specific to recurrent respiratory papillomatosis are lacking. The International Pediatric Otolaryngology Group (IPOG) issued the "JORRP consensus recommendations" in 2020 (hereafter referred to as the 2020 IPOG expert consensus).[9] While the publication provides certain guidance for clinical work, it neither represents a comprehensive diagnostic and treatment pathway nor a standard supported by multidisciplinary research. Consequently, there is an urgent need to develop evidence-based clinical practice guidelines tailored to China's national context. These guidelines would offer direction and standardization for clinical decision-making for patients with JORRP in China, promote the development of new treatment methods, and improve outcomes for patients nationwide.

PURPOSE

To establish a framework for decision-making in diagnosing and treating JORRP and offer guidance to medical professionals involved in its clinical practice.

TARGET POPULATION

These guidelines apply to patients aged 0–18 diagnosed with JORRP.

USERS

This guideline is intended for use by clinicians and teaching and research staff specializing in otolaryngology-head and neck surgery. Also, any other medical personnel can refer to this guideline.

RECOMMENDATION

As shown in Table 1, this guideline includes 12 clinical questions and 24 recommendations for diagnosing and treating JORRP. Furthermore, Figure S1 presents a flowchart designed to outline the diagnostic and therapeutic processes, based on these recommendations, with the aim of offering clear guidance for primary care physicians. Table 2 shows the quality of evidence and strength of recommendation grading using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.

CLINICAL QUESTIONS

Diagnosis questions

Clinical question 1: What clinical signs and symptoms should be considered in diagnosing JORRP?

Recommendations: Concerning symptoms, emphasis should be placed on hoarseness, particularly if lasting more than 2 months or showing progressive deterioration (evidence quality: A; recommendation strength: strong). Attention is advised for inspiratory dyspnea and wheezing (evidence quality: B; recommendation strength: weak).

Regarding signs, the focus should be placed on cyanosis, the three concave signs, and abnormal breath sounds, especially in severe cases and patients with lower airway lesions (evidence quality: B; recommendation strength: weak).

Evidence summary: We conducted a qualitative analysis of 29 studies[10–38] (n = 852) describing the signs and symptoms of children with JORRP. Studies included 14 case series (n = 717), one retrospective cohort study (n = 112), one case-control study (n = 10), and 13 case reports (n = 13). The most prevalent symptom was hoarseness (88.0%; 750/852). Of the 750 patients with hoarseness, 473 had clear documentation of the symptom duration, with 80.5% (381/473) lasting more than 2 months. Other commonly reported symptoms include varying degrees of dyspnea (25.7%; 219/852), wheezing (10.2%; 87/852), and chronic

TABLE 1 Summary of questions and recommendations

Questions	Recommendations
Diagnosis questions	
1. What clinical signs and symptoms should be considered in diagnosing JORRP?	Concerning symptoms, emphasis should be placed on hoarseness, particularly if lasting more than 2 months or showing progressive deterioration (1A). Attention is advised for inspiratory dyspnea and wheezing (2B). Regarding signs, focus should be placed on cyanosis, the three concave signs, and abnormal breath sounds, especially in severe cases and patients with lower airway lesions (2B).
2. Should all children with hoarseness combined with wheezing, laryngeal obstruction, or difficulty in breathing undergo flexible laryngoscopy?	It is recommended that all children with hoarseness combined with wheezing, laryngeal obstruction, or difficulty in breathing undergo flexible laryngopharyngoscopy once their vital signs are assessed and deemed stable (1A).
3. Which grading/staging standard should be used to evaluate the severity of JORRP?	The Derkay scoring system is strongly recommended as the primary tool for assessing the extent of the lesion and disease severity (1A). For children with JORRP lasting more than one year, it is recommended to distinguish between invasive and non-invasive JORRP based on clinical features. The criteria for invasive JORRP are as follows: total number of surgeries $\geq$10, average number of surgeries per year $\geq$4, distant spread to the lower airway, and children who need or have undergone tracheostomy (GPS).
4. What are the high-risk factors for JORRP recurrence?	Children with early-onset disease and HPV11 positivity are at higher risk of recurrence and warrant special attention (1B). Children from low socioeconomic backgrounds and those with a history of maternal condyloma acuminatum during pregnancy are more likely to relapse, and surveillance is recommended for such patients (2C).
Treatment questions	
5. How should we choose a preoperative airway assessment plan for children with JORRP?	Preoperative airway assessment should be performed for all children with JORRP (GPS). The degree of laryngeal obstruction is recommended as the primary indicator for preoperative airway assessment in children with JORRP (2C). Consideration should be given to the extent of lesions and number of previous surgeries, as well as the American Society of Anesthesiologists (ASA) physical status grading assessment of the overall condition (GPS).
6. How should we choose an anesthesia ventilation scheme for children with JORRP?	Endotracheal intubation and mechanical ventilation are recommended as the ventilation method for general anesthesia during surgery in children with JORRP (1B). Jet ventilation can be considered a supplementary anesthesia ventilation method (2B).
7. What are the factors (e.g., tumor location, size, or degree of laryngeal obstruction) to be considered when selecting the timing of surgery?	Surgery should be performed as soon as possible when symptoms of laryngeal obstruction occur (1C). Surgery should be actively performed when the lesion involves the trachea (2C).
8. How can we approach lesion removal (breadth and depth) during surgical treatment?	The depth of lesion removal should extend to the base of the tumor (submucosal layer), with a focus on preserving the vocal ligaments (GPS). The decision to perform bilateral surgery simultaneously should be based on lesion size and surgical method, with careful attention to safeguarding the anterior commissure during surgery to minimize postoperative vocal cord adhesion (GPS).
9. How can surgical instruments (cold steel, laryngeal microdebriders, CO_2 lasers, or radiofrequency ablation) be utilized in the treatment of JORRP?	It is recommended to use a CO_2 laser and/or laryngeal microdebrider for JORRP surgical treatment according to the institutional resources and the patient's condition (1B).
10. What are the indications for tracheostomy in patients with JORRP?	Tracheostomy should be avoided as much as possible in children with JORRP (1B). For patients with JORRP who have undergone tracheostomy, the tube should be removed as soon as possible after the patient is stable and the condition/respiratory situation has been fully evaluated (1C). Tracheostomy should be performed in patients with JORRP who have grade II or higher laryngeal obstruction, cannot undergo surgery immediately, or in those whose symptoms cannot be relieved by surgery (2B).
11. What is the optimal timing and frequency for postoperative follow-up for patients with JORRP?	It is recommended that patients seek medical attention immediately after laryngeal obstruction occurs, and timely medical evaluation should be sought when respiratory symptoms such as hoarseness, rough breathing, and snoring occur (GPS). It is recommended that patients undergo regular follow-ups, and the follow-up frequency be determined individually based on specific patient factors, such as age, HPV genotyping, and number of previous surgeries in clinical practice (GPS).
12. What are the indications, effectiveness, and safety profile of bevacizumab as an adjunct treatment for JORRP?	For patients with rapid disease progression, frequent surgical interventions, and lower airway spread, bevacizumab can be considered an adjunctive treatment (2D).

Abbreviations: GPS, good practice statement; HPV, human papillomavirus; JORRP, juvenile-onset recurrent respiratory papillomatosis.

TABLE 2 Grading of quality of evidence and strength of recommendation

Category	Description
Quality of evidence	
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate (B)	We are moderately confident in the effect estimate: the true effect is presumably close to the estimate of the effect, but it might be substantially different.
Low (C)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low (D)	We have very little confidence in the effect estimate: the true effect is presumably substantially different from the estimate of effect.
Strength of recommendation	
Strong (1)	The advantages of intervention considerably outweigh the disadvantages, or disadvantages of intervention considerably outweigh the advantages
Weak (2)	The advantages of intervention may outweigh the disadvantages, or disadvantages of intervention may outweigh the advantages
Good practice statement (GPS)	Recommendations based on indirect evidence or expert opinion/experience

cough (7.3%; 62/852), as well as hemoptysis, chest pain, fever, expectoration of meaty tissue, difficulty in swallowing, voice loss/weak voice, delayed speech development, and nocturnal awakening.

Signs of JORRP in children are often challenging to discern, with only 16.4% (36/219) of children with varying degrees of dyspnea showing typical signs of inspiratory dyspnea, such as cyanosis, three concave signs, barrel chest, and abnormal breath sounds. The 2020 IPOG consensus identified progressive hoarseness, wheezing, and respiratory distress as common symptoms.[9] A 2008 systematic review describing the incidence of lung involvement in JORRP found that lesions can invade the lower respiratory tract and reported that 28.9% (22/76) of affected children presented with symptoms such as cough, hemoptysis, and chest pain.[39]

Justification: This recommendation is based on evidence from qualitative research and commonly occurring symptoms and signs from the previous consensus. Notably, it is suggested that attention be paid to children with hoarseness lasting more than 2 months or showing progressive deterioration. However, combined with previous clinical experience, it is suggested that medical attention be sought after 3–4 weeks of hoarseness, regardless of the type of lesion, and the focus on the degree of hoarseness and dyspnea should be in the context of the patient's age. Overall, these symptoms should be analyzed in conjunction with the specific situation of the child to avoid misdiagnosis.

Signs of JORRP, such as inspiratory dyspnea, wheezing, the three concave signs, and cyanosis, should warrant attention from clinicians. Combined with the results of expert interviews and the opinions of experts in the guideline development group, the frequency of lower airway lesions in children with JORRP was relatively low. Also, the signs of lower airway involvement (such as barrel chest and abnormal breath sounds) were not specific for JORRP. They should be combined with medical history and physical examinations to arrive at a diagnosis. These guidelines advocate for a comprehensive approach combining single or multiple symptoms and signs, laryngoscopy, and pathological biopsy to improve diagnostic accuracy.

Clinical question 2: Should all children with hoarseness combined with wheezing, laryngeal obstruction, or difficulty in breathing undergo flexible laryngopharyngoscopy?

Recommendations: It is recommended that all children with hoarseness combined with wheezing, laryngeal obstruction, or difficulty in breathing undergo flexible laryngopharyngoscopy once their vital signs are assessed and deemed stable (evidence quality: A; recommendation strength: strong).

Evidence summary: The guideline working group performed a qualitative analysis, reviewing 19 papers (n = 4542) relevant to "Children with hoarseness, wheezing or dyspnea symptoms undergo flexible laryngopharyngoscopy (i.e., electronic/fiber laryngoscopy)". Articles reviewed include one expert consensus, 11 case series (n = 4534),[23, 31, 40–48] and seven case reports (n = 8).[20, 21, 25, 26, 49–51] Our findings showed that among the 3790 children (3790/4542, 83.44%) with simple hoarseness, 117 (3.09%) were diagnosed with JORRP after examination with an electronic/fiber laryngoscope, while of the 752 children with hoarseness combined with wheezing, laryngeal obstruction, or respiratory distress, 82 (82/752, 10.90%) were diagnosed with JORRP post-examination. Among them, 27 cases were diagnosed by

electronic/fibrous laryngoscopy, and 55 cases were diagnosed by direct laryngoscopy under general anesthesia. Compared to patients with simple hoarseness, those with hoarseness combined with wheezing or dyspnea had a higher prevalence of JORRP (3.09% vs. 10.90%, respectively). The 2020 IPOG expert consensus recommends that a flexible fiberoptic laryngoscopy be used for preliminary diagnosis in patients with hoarseness, wheezing, and dyspnea after performing a clinical examination and confirming the stability of their vital signs and blood oxygen saturation. Furthermore, a pathological biopsy should be performed under a direct laryngoscope/bronchoscope to further clarify the diagnosis.[9]

Justification: This recommendation is evidence-based and aligns with the 2020 IPOG expert consensus recommendation.[9] Supported by expert interviews and the consensus of the guideline development group, the degree of concordance was 95.24%. For infants and children with clinical symptoms of hoarseness, wheezing, and dyspnea, diagnosis cannot rely solely on medical history, necessitating auxiliary examinations for differentiation. Flexible laryngopharyngoscope, a fundamental tool in otolaryngology and head and neck surgery, has the advantages of visibility, intuitiveness, three-dimensionality, and ease of operation. It can assist doctors in the diagnosis of patients with such clinical manifestations, so it can be used as the first test for the diagnosis of JORRP. For some children with poor coordination, unsatisfactory vocal cord exposure, or emergency situations, direct laryngoscopy under general anesthesia can be selected to avoid delayed diagnosis. Primary care physicians should promptly refer patients based on their condition and available medical resources.

Clinical question 3: Which grading/staging standard should be used to evaluate the severity of JORRP?

Recommendations: The Derkay scoring system is strongly recommended as the primary tool for assessing the extent of the lesion and disease severity (evidence quality: A, recommendation strength: strong).

For children with JORRP lasting more than one year, it is recommended to distinguish between invasive and noninvasive JORRP based on clinical features. The criteria for invasive JORRP are as follows: total number of surgeries ≥10, average number of surgeries per year ≥4, distant spread to the lower airway, and children who need or have undergone tracheostomy (good practice statement [GPS]).

Evidence summary: The guideline working group conducted a literature search and identified 23 articles about the grading/staging evaluation methods for children with JORRP. These included one expert consensus, 17 retrospective cohort studies ($n = 1018$), three case reports ($n = 4$), one randomized controlled trial ($n = 34$), and one review. Previously, six methods of disease staging/grading have been summarized: Kashima et al.,[52] Lusk et al.,[53] Derkay et al.,[54] Pasquale et al.,[55] Buchinsky et al.,[56] and Moreddu in 2019.[57]

In addition to the six articles that first proposed the evaluation methods mentioned above and one expert consensus, the guidelines working group summarized the use of these grading/staging methods in the remaining 16 original articles identified. Our results showed that the grading/staging method proposed by Derkay in 1998 (referred to as Derkay's score) was the most frequently used in the literature, utilized by a total of 8 articles,[58–65] followed by the method proposed by Buchinsky in 2008, which was utilized in five retrospective cohort studies ($n = 520$) and one case report ($n = 2$).[3, 58, 59, 66–68] Buchinsky divided JORRP into invasive and noninvasive groups and studied the treatment effect of drugs or related risk factors. Among the studies that used the Derkay's score, two retrospective cohort studies evaluated the relationship between the Derkay's score and disease severity. A 2023 article[59] demonstrated that Derkay's score had a moderate positive correlation with the average number of surgeries per year ($r = 0.588$, $P = 0.001$) and a weak positive correlation with the total number of surgeries ($r = 0.280$, $P < 0.01$). Receiver operating characteristic (ROC) curve analysis showed that the best cut-off value for Derkay's score was 14.55, and its area under the curve (AUC) was 0.768 (95% confidence interval [CI]: 0.672, 0.864). Generally, for every one-point increase in Derkay's score, the probability of invasiveness increases to about 1.2 times (95% CI: 2.237, 2.645).[59] Another study published in 2004 by Derkay et al.[62] reported the scores of 17 children according to the interval between surgeries. Their results suggested that for every one-point increase in Derkay's score, the interval between surgeries was shortened by 4 days. Also, when comparing the group of children with a score greater than 20 with those with a score less than 20, the average interval between surgeries was shortened by 120 days ($P = 0.005$).[62]

According to the 2020 IPOG Expert Consensus, Derkay's score is the most common staging method for RRP, and follow-up time can be planned based on the score results, 37% of experts in the consensus always or often use this score; At the same time, the consensus refers to the evaluation method proposed by Buchinsky in 2008, which considers the average number of surgeries per year ≥4 or the presence of lower airway distant transmission as one of the criteria for whether systemic adjuvant therapy should be applied.[9]

Justification: The evaluation of disease stage and grade in children with JORRP helps doctors to accurately assess disease severity and make individualized plans, including

selection of when to operate, formulation of surgery plans, and arrangement of follow-up time for different children with JORRP. Owing to factors such as the continuous improvement in drug treatment and surgical techniques, different levels of medical care in hospitals in different regions, and different standards of surgical timing in different regions and hospitals, there is some controversy regarding the use of the number of surgeries for disease grading. Some hospitals use ≥3 surgeries as the threshold for determining invasive and non-invasive diseases.[69, 70] However, literature utilizes ≥4 as the threshold, so this guideline aligns with the standard proposed by Buchinsky in 2008 to divide JORRP into invasive or non-invasive groups. Although Derkay's score was the most frequently used in previous studies, one of its limitations is that it requires complete exposure of the lesion. Therefore, it is generally obtained during surgery or when reviewing the surgical video and cannot be derived following laryngoscopy before surgery.

Clinical question 4: What are the high-risk factors for JORRP recurrence?

Recommendations: Children with early onset disease and Human Papillomavirus Type 11 (HPV11) positivity are at higher risk of recurrence and warrant special attention (evidence quality: B; recommendation strength: strong).

Children from low socioeconomic backgrounds and those with a history of maternal condyloma acuminatum during pregnancy are more likely to relapse, and surveillance is recommended for such patients (evidence quality: C; recommendation strength: weak).

Evidence summary: The guideline working group conducted a systematic review of 20 cohort studies ($n = 3435$), comprising 17 retrospective[3, 58, 66, 69–82] and 3 prospective cohort studies[56, 83, 84] that reported four main risk factors for JORRP disease recurrence. The results revealed the following:

(1) Age at first onset (16 studies, $n = 2702$): All studies found that early age of disease onset is a high-risk factor for recurrence. Meta-analysis of two studies with available data for extraction showed more aggressive (relative risk [RR] = 2.40; 95% CI: 1.39, 4.15; $P = 0.002$),[69] and shorter interval between surgeries (RR = −123.80; 95% CI: −168.72, −78.88; $P < 0.00001$)[78] in patients less than 4 years old at first-onset than the group with age greater than 4 years.

(2) HPV typing (10 studies, $n = 1509$): All studies reported that HPV11 positivity is a significant risk factor for disease recurrence. Meta-analysis of four articles revealed more invasiveness (RR = 1.24; 95% CI: 1.12, 1.37; $P < 0.0001$),[3, 56, 66] higher tracheostomy rates (RR = 6.74; 95% CI: 0.84, 53.84; $P = 0.07$),[84] and elevated rates of tracheal spread (RR = 5.39; 95% CI: 1.72, 16.93; $P = 0.004$)[84] in patients positive for HPV11 compared to those positive for HPV6.

(3) Socioeconomic status (three studies, $n = 132$): Socioeconomic status was indicated by type of medical insurance type, residential area, and self-reported assessment of economic status, while severity/invasiveness of disease was obtained using Derkay's score, number/frequency of surgeries, and lower airway spread or a combination of two or three of these indicators. Notably, all results suggested that low socioeconomic status was consistently associated with disease recurrence.[77, 81, 84]

(4) History of maternal condyloma acuminatum during pregnancy (four studies, $n = 377$): These four studies utilized varying outcome indicators; however, all suggest that a maternal history of condyloma acuminatum during pregnancy is a high-risk factor for disease recurrence. Their findings are as follows: compared to their counterparts, children whose mothers have a history of condyloma acuminatum exhibit higher severity (odds ratio [OR] = 12.05; 95% CI: 0.97, 149; $P = 0.05$),[77] elevated Derkay's score ($P < 0.006$),[84] increased frequency of surgeries ($P < 0.001$),[73] and a 2.2 times greater odds of an invasive disease ($P = 0.06$).[3] Therefore, the results of the systematic review conducted by our working group suggest that early age at onset and HPV11 positivity are important risk factors for JORRP recurrence. At the same time, low socioeconomic status and maternal history of condyloma acuminatum during pregnancy are related to JORRP recurrence.

A systematic review of 32 studies conducted in 2014[85] revealed age at onset, HPV genotype, socioeconomic status, maternal history of condyloma acuminatum during pregnancy, host genetics, and immune response as risk factors for JORRP recurrence. Among these, early age of onset and HPV11 positivity emerged as the most important risk factors affecting the severity of JORRP. At the same time, low socioeconomic status was also found to correlate with the severity of the disease. These findings are consistent with the conclusions drawn from the systematic review conducted by the guideline working group. Regarding the relationship between maternal history of condyloma acuminatum during pregnancy and JORRP, the study highlighted a 231-fold increased risk (OR = 231; 95% CI: 135.3, 395.9) but did not indicate its impact on disease severity.

Justification: Early age of onset and HPV11 positivity are the main risk factors for disease recurrence. Studies have demonstrated that the clinical course of JORRP is more closely related to the age at first onset than to the HPV type.[3, 56] Clinicians should pay close attention to patients at an early age of onset and institute surveillance to detect

disease recurrence. HPV genotyping can be included in routine postoperative pathological examinations to assess the risk of recurrence. Although low socioeconomic status is an established high-risk factor for disease recurrence, timely medical treatment may mitigate its impact.[85] Maternal history of condyloma acuminatum during pregnancy elevates the risk of recurrence, suggesting that preventive measures in women of childbearing age may be an effective means of reducing disease burden.[85]

Treatment questions

Clinical question 5: How should we choose a preoperative airway assessment plan for children with JORRP?

Recommendations: Preoperative airway assessment should be performed for all children with JORRP (GPS).

The degree of laryngeal obstruction is recommended as the primary indicator for preoperative airway assessment in children with JORRP (evidence quality: C; recommendation strength: weak).

Consideration should be given to the extent of lesions and number of previous surgeries, as well as the American Society of Anesthesiologists (ASA) physical status grading assessment of the overall condition (GPS).

Evidence summary: The guideline development working group included two retrospective cohort studies ($n = 51$)[86, 87] in their systematic review of preoperative anesthesia intubation for children with JORRP. A comparison of single intubation success rates between children with and without laryngeal obstruction revealed a higher success rate among those without laryngeal obstruction (RR = 0.66; 95% CI: 0.47, 0.92; $P = 0.01$). This underscored the significance of assessing laryngeal obstruction in assessing the risk of anesthesia.

Qualitative research conducted by the guideline development working group yielded the following results:

(1) Twenty-eight studies related to the preoperative airway assessment method for children with JORRP ($n = 2646$)[86–113] were included, comprising one randomized controlled trial (RCT) ($n = 40$), two crossover RCTs ($n = 132$), one prospective cohort study ($n = 23$), four retrospective cohort studies ($n = 153$), one cross-sectional study ($n = 1225$), 18 retrospective case series reports ($n = 1072$), and one case report.

(2) Four pre-anesthesia assessment indicators were reported: degree of laryngeal obstruction, distribution of lesions, ASA grading, and number of previous surgeries. The most commonly used airway assessment method was the degree of laryngeal obstruction, followed by ASA grading, and the number of previous surgeries (Table 3).

The guideline development working group designed a questionnaire pertaining to clinical queries regarding JORRP and distributed it to senior anesthesiologists in 28 medical units, with 34 responses returned. The survey results revealed the following:

(1) Unanimous agreement on the importance of preoperative airway assessment for children with JORRP undergoing general anesthesia (100% support rate, 34/34). (2) Preoperative airway assessment indicators favored by respondents included: degree of laryngeal obstruction (100%, 34/34), number of previous surgeries (91.18%, 31/34), ASA grade (88.24%, 30/34), extent of lesions (88.24%, 30/34), and number of previous surgeries (76.47%, 26/34). Anesthesiologists uniformly acknowledge the pivotal role of airway assessment prior to surgery in children with JORRP, with particular emphasis placed on the degree of laryngeal obstruction. Additionally, ASA grading, number of previous surgeries, and range of lesions can be used as supplementary references.

Justification: This recommendation is mainly based on quantitative and qualitative research conducted by the guideline working group, coupled with insights garnered from clinical questionnaires to experts and the opinions of experts in the guideline working group. It is recommended that all children with JORRP undergo preoperative airway assessment and that the degree of laryngeal obstruction be used as the main method of assessment. Previous studies lacked a standardized preoperative airway assessment method for children with JORRP. The degree of laryngeal obstruction can provide insight into the extent of airway obstruction due to lesions, aiding in assessing the risk of anesthetic intubation. In addition, the 2022 American Society of Anesthesiologists Difficult Airway Management Practice Guidelines recommend adherence to ASA basic anesthesia monitoring standards before, during, and immediately after airway management.[114] Airway assessment should be tailored to individual circumstances and clinical requirements at the local hospital and can be combined with ASA grading, lesion range, and the number of previous surgeries as references.

Clinical question 6: How should we choose an anesthesia ventilation scheme for children with JORRP?

Recommendations: Endotracheal intubation and mechanical ventilation are recommended as the ventilation method for general anesthesia during surgery in children with JORRP (evidence quality: B; recommendation strength: strong).

TABLE 3 Distribution of different airway assessment plans in 28 studies

Airway assessment plan of JORRP	No. of studies, *n* (%)	Sample size, *n* (range)
Degree of laryngeal obstruction	6 (20.7)	460 (28–142)
ASA grading	2 (6.9)	59 (23–36)
Degree of laryngeal obstruction + distribution of lesions	4 (13.8)	345 (23–202)
Degree of laryngeal obstruction + ASA grading	6 (20.7)	1395 (20–1225)
Degree of laryngeal obstruction + number of previous surgeries	2 (6.9)	19 (1–18)
Distribution of lesions + ASA grading	1 (3.4)	25
Degree of laryngeal obstruction + distribution of lesions + ASA grading	1 (3.4)	28
Degree of laryngeal obstruction + distribution of lesions + number of previous surgeries	2 (6.9)	180 (32–148)
Degree of laryngeal obstruction + ASA grading + number of previous surgeries	3 (10.3)	95 (9–58)
Degree of laryngeal obstruction + distribution of lesions + ASA grading + number of previous surgeries	1 (3.4)	40

Note: Among the 28 studies, 25 used the degree of airway obstruction as a preoperative anesthesia assessment indicator for patients with JORRP, resulting in a utilization rate of 89.3% (25/28). JORRP, juvenile-onset recurrent respiratory papillomatosis; ASA, American Society of Anesthesiologists.

Jet ventilation can be considered a supplementary anesthesia ventilation method (evidence quality: B; recommendation strength: weak).

Evidence summary: The guideline development working group conducted qualitative research, reviewing 57 studies related to the anesthesia ventilation method for children with JORRP (n = 3285), comprising two prospective randomized crossover trials (n = 132),[101, 113] five RCTs (n = 180),[108, 115–118] two retrospective cohort studies (n = 102),[95, 110] one prospective cohort study (n = 23),[88] two cross-sectional studies (n = 1250),[99, 119] 35 retrospective case series reports (n = 1588), and ten case reports (n = 10). Five anesthesia ventilation methods were identified in the reviewed literature (jet ventilation, mechanical ventilation, spontaneous breathing ventilation, intermittent positive pressure ventilation, and transnasal humidified rapid insufflation ventilatory exchange), with mechanical ventilation being the most frequently utilized method for ventilation during general anesthesia (22/57, 38.6%). As shown in Table 4, this was followed by jet ventilation (11/57, 19.3%). Three types of airway tools (endotracheal intubation, nasal cannula, and other airway cannula types) were identified from the literature, with endotracheal intubation being the most commonly used tool for general anesthesia (45/57, 78.9%).

Two studies compared the safety of endotracheal intubation and mechanical ventilation with spontaneous breathing or high-frequency ventilation. A prospective randomized crossover trial (n = 104) found that the oxygen saturation at the end of surgery in the spontaneous breathing group (n = 52) was lower than that in the endotracheal intubation group (n = 52) (97.13% ± 3.25% vs. 99.63% ± 0.68%).[101] Additionally, the end-tidal CO_2 partial pressure and the rate of laryngeal spasm were higher in the spontaneous breathing group (42.06 ± 4.59 mmHg vs. 39.33 ± 1.61 mmHg; 19.2% vs. 0), and some children in the spontaneous breathing group had postoperative apnea, which was not observed in the endotracheal intubation group (28.8% vs. 0). Another retrospective cohort study (n = 40) found that 30% (6/20; OR = 18.38; 95% CI: 0.96, 352.57) of children in the high-frequency ventilation group had complications such as apnea, laryngeal spasm, and decreased blood oxygen levels, while no such complications occurred in the endotracheal intubation group (n = 20).[95]

One RCT (n = 40) utilized jet ventilation as a ventilation method for JORRP and found that the oxygen saturation at the end of surgery in the jet ventilation group (n = 20) was significantly higher than that in the intermittent group (n = 20) (99.3% ± 0.9% vs. 94.8% ± 2.5%).[108] Additionally, the end-tidal CO_2 partial pressure was higher than that in the intermittent group (48.9 ± 2.5 mmHg vs. 64.5 ± 4.9 mmHg), and the recovery time was shorter than that in the intermittent group (14.9 ± 2.8 min vs. 20.8 ± 2.5 min).

Justification: Based on the obtained evidence and input from the guideline development working group, as well as considering the peculiarities of China, we recommend endotracheal intubation plus mechanical ventilation as the ventilation method for general anesthesia in children with JORRP. Jet ventilation can be considered as a supplementary ventilation method, depending on the conditions of each institution. The 2020 IPOG expert consensus,[9] which was conducted in the United States, Canada, Australia, and other countries, pointed out that there is a large difference in the choice of anesthesia ventilation methods, which can

TABLE 4 Combination and frequency of different ventilation in 57 studies

Ventilation scheme	Number of studies, *n* (%)	Sample size, *n* (range)
Jet ventilation[a]	12 (21.1)	466 (1–142)
Mechanical ventilation[a]	22 (38.6)	534 (1–148)
Mechanical ventilation[b] (transnasal humidified rapid insufflation ventilatory exchange[c])	1 (1.8)	28
Intermittent positive pressure ventilation[a]	5 (8.8)	192 (22–52)
Spontaneous breathing ventilation[a]	3 (5.3)	232 (1–202)
Mechanical ventilation[a] or spontaneous breathing ventilation[a]	6 (10.5)	333 (28–104)
Mechanical ventilation[a] or jet ventilation[a]	3 (5.3)	78 (11–40)
Mechanical ventilation[b] (jet ventilation[c]) or intermittent positive pressure ventilation[a]	2 (3.5)	1265 (40–1225)
Mechanical ventilation[b] (intermittent positive pressure ventilation[c] + spontaneous breathing ventilation[d])	1 (1.8)	70
Mechanical ventilation[a] or mechanical ventilation[b] (spontaneous breathing ventilation[c]) or spontaneous breathing ventilation[a]	2 (3.5)	87 (25–62)

Note: [a]ventilation method is used throughout the surgery; [b]method is used only when tumors are removed in the glottic and supraglottic regions during surgery; [c]method is used only when tumors are removed in the subglottic region during surgery; [d]method is used only when combined tumors are removed after clearance during surgery.

be selected based on personal preferences. The consensus results showed that 94% chose spontaneous ventilation, 94% did not choose jet ventilation, and 90% did not choose endotracheal intubation; however, there were no clear data to support the specific reasons. During general anesthesia and surgery for patients with JORRP, the anesthesiologist and otolaryngologist share the airway. Therefore, the ventilation method must satisfy both the anesthesia depth and provide space for the surgeon to manipulate. Compared to spontaneous breathing and jet ventilation, endotracheal intubation provides direct access to the lower airway, ensuring stable oxygen delivery. Also, endotracheal intubation is a standard procedure in all hospitals in China that perform surgery, and it provides a relatively safe option to perform JORRP surgery. Although it may occupy a certain field of view and some operating space, choosing a suitable intubation technique and position during surgery greatly reduces its interference with the procedure. Jet ventilation, initially developed for use in adult laryngeal surgery,[120] has been adapted for pediatric use, including airway-related disease treatment. It offers advantages such as clear surgical field visibility and guaranteed oxygen supply without intubation; however, it also has disadvantages such as carbon dioxide retention, cardiovascular strain, and increased risk of aspiration of intraoperative bleed into the lower airway.[121, 122] While newer technologies like high-frequency superimposed jet ventilation have fewer complications and show promise with improved ventilation and oxygenation,[123] their adoption in China remains limited, and there is still a lack of standardized, large-sample, multi-center research to support its recommendation. Considering the potential risks associated with traditional high-frequency jet ventilation, it is not chosen by most experts, and the guideline development working group advises against the routine use of jet ventilation. Instead, it may be considered as a combined ventilation method under specific conditions.

In addition, a prospective randomized crossover trial in 2023 introduced transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) as a novel technology for general anesthesia during surgery in children with JORRP.[113] The results suggest that the use of THRIVE during surgery significantly prolongs apnea time ($P < 0.001$) and reduces the rate of CO_2 change ($P < 0.001$), showing promise for future applications. However, large-scale data supporting its efficacy and safety are lacking.

Clinical question 7: What are the factors (e.g., tumor location, size, or degree of laryngeal obstruction) to be considered when selecting the timing of surgery?

Recommendations: Surgery should be performed as soon as possible when symptoms of laryngeal obstruction occur (evidence quality, C; recommendation strength, strong).

Surgery should be actively performed when the lesion involves the trachea (evidence quality, C; recommendation strength, weak).

Evidence summary: The guideline working group reviewed nine retrospective cohort studies ($n = 664$) and one case report ($n = 1$) that provided insights into the optimal timing of JORRP surgery. Among these, three retrospective cohort studies ($n = 211$) described the relationship between laryngeal obstruction and the timing of surgery.[60, 95, 119] For instance, the results of the retrospective cohort study in 2014 ($n = 73$)[60] showed that among 289 surgeries, children with Grade III and IV laryngeal obstruction (19/60, 31.7%) had a significantly

higher incidence of perioperative adverse events compared to those with Grades I and II (5/229, 2.18%). Hence, this suggests that surgery should be performed when the laryngeal obstruction symptoms do not exceed Grade II. A retrospective cohort study in 2016 ($n = 118$)[119] identified the severity of laryngeal obstruction as a high-risk factor for tracheotomy post-surgery ($\chi^2 = 32.369$, $P < 0.001$). Similarly, another retrospective cohort study conducted in 2012 ($n = 208$) reported that out of 208 patients, 46 with tracheal involvement had shorter surgery intervals, more surgeries, and a higher rate of tracheotomy ($\chi^2 = 98.144$, $P < 0.001$) than those without tracheal involvement.[124] Therefore, it is suggested that surgery be performed when the disease involves the trachea.

Justification: The presence of clinical symptoms is the key to determining the timing of surgery. This guideline recommends initiating surgery based on "the occurrence of laryngeal obstructive symptoms" and "lesions involving the trachea". Previous studies suggest that the HPV virus may be latent in the epithelial cell basal layer during the early stages of infection. Immune function decline or mucosal injury can activate epidermal growth factors, inhibiting the activity of tumor suppressor proteins and leading to excessive proliferation of infected cells.[125] Frequent surgeries may exacerbate tumor growth. Therefore, surgery frequency should be minimized to ensure the child's safety and minimize repetitive surgical trauma. Whether surgery is warranted for children with recurrent JORRP who only have hoarseness without breathing-related symptoms remains controversial. The 2020 IPOG expert consensus[9] highlights the importance of voice quality and states that hoarseness should be treated. Combining the opinions of the guideline development working group experts, we advocate that for older children with social needs, surgery can be considered when the hoarseness significantly impacts life and the parents strongly desire treatment. Regarding the use of Derkay's score to determine the timing of surgery, four studies have been published,[59, 61–63, 126] comprising five retrospective cohort studies ($n = 210$) and one case report ($n = 1$). Results show that Derkay's score is related to the frequency of surgery but does not clearly influence the surgery timing. Also, incomplete exposure of the lesion during laryngoscopy before surgery will lead to inaccurate Derkay's scores. Therefore, using Derkay's score or other anatomical scores to assess the timing of surgery is not recommended.

Clinical question 8: How can we approach lesion removal (breadth and depth) during surgical treatment?

Recommendations: The depth of lesion removal should extend to the base of the tumor (submucosal layer), with a focus on preserving the vocal ligaments (GPS).

The decision to perform bilateral surgery simultaneously should be based on lesion size and surgical method, with careful attention to safeguarding the anterior commissure during surgery to minimize postoperative vocal cord adhesion (GPS).

Evidence summary: The guideline development working group analyzed 16 studies (five retrospective cohort studies ($n = 476$), eight case series reports ($n = 349$), one cross-sectional study ($n = 112$), and two reviews) investigating the breadth and depth of JORRP lesion removal. Four studies discussed the range of lesion removal, suggesting staged surgery for lesions involving the anterior commissure, with two studies specifically recommending CO_2 laser surgeries[127, 128] and the other two not specifying the surgical method.[129, 130] Regarding depth, 11 out of 13 (84.6%) suggested reaching the base of the tumor (submucosal layer) during surgery,[131–140] utilizing various methods such as cold instruments, microdynamic cutting, suction drills, and CO_2 lasers. One of them emphasized that the depth of excision should be shallow in the basal layer.[141] The remaining two studies (16.67%, 2/12) suggested that removal depth should reach the mucosal layer, utilizing CO_2 lasers.[128, 142]

In addition to the literature review, the working group sent two rounds of Delphi questionnaires with relevant experts. The first round, with 21 responses, achieved consensus on "complete removal of lesions involving the larynx and trachea at one time (80% consensus)". The experts did not reach a consensus on the other opinions, including "staged surgery for lesions involving the anterior commissure (55% consensus)" and "one-time surgery for lesions involving the anterior commissure and bilateral vocal cords (40% consensus)". For the recommendation on depth of lesion removal, consensus was reached on "the depth of lesion resection should be at the base of the tumor (submucosa) with attention to protecting the vocal ligaments (100% consensus)". After modifying the relevant recommended opinions based on expert opinions, a second round of questionnaires was sent out, and 23 responses were returned. A consensus was reached on "Performing bilateral surgery simultaneously depends on the range of the lesion and surgical method adopted. During surgery, attention should be paid to protecting the anterior commissure to minimize postoperative vocal cord adhesions (consensus 91.3%)."

Justification: Considerable controversy exists surrounding the breadth and depth of lesion removal in JORRP, and there is a lack of reliable clinical data to conclusively settle the debate. This recommendation is based mainly on the results of the expert questionnaires, combined with the opinions of the expert in the guideline

development working group. Given the high recurrence and invasiveness of JORRP, surgery should aim to remove the tumor as thoroughly as possible to reduce recurrence while avoiding postoperative adhesion and interference with vocal function. The layered structure of the vocal cords has fewer fibroblasts in Reinke's space, resulting in less extracellular matrix production. Thus, completing surgery in the superficial layer of Reinke's space can minimize scar formation.[131] In addition, special protection of the vocal ligaments (middle intrinsic layer) is required during the operation to avoid damage and maintain basic vocal function.[143] For children with laryngeal adhesions, the possibility of increased adhesion and parental wishes should be assessed before and during surgery, and a comprehensive evaluation of these factors should be used to decide whether adhesiolysis surgery should be performed at the same time.

Clinical question 9: How can surgical instruments (cold steel, laryngeal microdebriders, CO_2 lasers, or radiofrequency ablation) be utilized in the treatment of JORRP?

Recommendations: It is recommended to use a CO_2 laser and/or laryngeal microdebrider for JORRP surgical treatment according to the institutional resources and the patient's condition (evidence quality: B; recommendation strength: Strong).

Evidence summary: The systematic review conducted by the guideline development working group included 14 studies employing two or more of the following instruments: CO_2 lasers, cold steel, or laryngeal microdebriders to treat JORRP, and simultaneously analyzed their treatment efficacy. Original data could not be extracted for three of these studies for statistical analysis, leaving a total of 11 studies (nine retrospective cohort studies[110, 133, 136, 144–149] and two randomized controlled trials[55, 150]; $n = 499$) for consideration. Four studies ($n = 266$) were included in a meta-analysis comparing the treatment outcomes of CO_2 laser and cold steel. The use of CO_2 laser was associated with a longer recurrence interval ($P < 0.05$),[147] lower recurrence rate (RR = 0.60; 95% CI: 0.46, 0.79; $P = 0.0003$),[133, 147, 149, 150] and higher cure rate (RR = 1.41; 95% CI: 1.14, 1.76; $P = 0.002$)[133, 149, 150] than cold steel in treating JORRP. Four articles ($n = 86$) compared the treatment outcomes of CO_2 laser and microdebrider. Results of a meta-analysis of three retrospective cohort studies suggested no statistically significant difference between the two surgical instruments in recurrence rate (RR = 1.08; 95% CI: 0.65, 1.80; $P = 0.76$) and incidence of complications (RR = 13.44; 95% CI: 0.85, 211.95; $P = 0.06$).[144–146] Also, one RCT[55] found no statistically significant difference in the improvement of voice quality post-surgery between patients who used CO_2 laser and those who used microdebrider ($P < 0.388$). However, the operation time with a microdebrider was significantly shorter than when the CO_2 laser ($P < 0.05$) was used, and the total surgical cost was lower ($899.15 vs. $1446.85). Three articles ($n = 147$) were included in a meta-analysis comparing the treatment outcomes of microdebrider and cold steel and no statistically significant difference was observed in recurrence rate (RR = 0.92; 95% CI: 0.84, 1.01; $P = 0.09$) and cure rate (RR = 2.41; 95% CI: 0.78, 7.43; $P = 0.13$)[110, 136, 148] between the two methods. However, the microdebrider exhibited a higher remission rate (RR = 5.76; 95% CI: 1.74, 19.02; $P = 0.004$),[148] lower incidence of complications (RR = 0.16; 95% CI: 0.07, 0.37; $P < 0.0001$),[136, 148] and a higher rate of postoperative voice quality improvement (RR = 2.31, 95% CI: 1.49, 3.60; $P < 0.0002$)[136] than cold steel.

The 2020 IPOG expert consensus did not provide a recommendation on the choice of surgical method,[9] suggesting that clinicians should base their decision on preference while ensuring maximal preservation of the laryngeal structure during lesion removing.

Note: *Cure is defined as no tumor recurrence in the specific follow-up period of the included study; remission is defined as a decrease in the number of recurrences, a reduction in the range of the tumor, or a reduction in hoarseness in the specific follow-up period of the included study; the follow-up period for the above definitions was >6 months.

Justification: Surgical excision is the first choice of treatment for patients with JORRP. Currently, no local or international consensus or guidelines exist regarding the choice of surgical instruments. This recommendation is confirmed through a systematic review of surgical instruments for the treatment of JORRP that demonstrates that CO_2 laser or microdebrider is better than cold steel. However, no obvious difference in treatment outcomes was found between CO_2 laser and microdebrider. Thus, each institution can choose appropriate surgical instruments for clinical diagnosis and treatment based on the availability of medical resources and the child's condition. Concerning the use of the cold plasma knife, the working group systematically reviewed eight studies describing patients with RRP treated with this instrument but could not completely extract clinical data on its use in pediatric patients. Hence, high-quality evidence for the application of the cold plasma knife in the treatment of JORRP is lacking. Moreover, the 2020 IPOG expert consensus stated that 70% of experts rarely utilize the cold plasma knife.[9] Further independent and high-quality research is required to ascertain the efficacy of the cold plasma knife in the treatment of children.

Clinical question 10: What are the indications for tracheostomy in patients with JORRP?

Recommendations: Tracheostomy should be avoided as much as possible in children with JORRP (evidence quality: B; recommendation strength: strong).

For patients with JORRP who have undergone tracheostomy, the tube should be removed as soon as possible after the patient is stable and the condition/respiratory situation has been fully evaluated (evidence quality: C; recommendation strength: strong).

Tracheostomy should be performed in patients with JORRP who have grade II or higher laryngeal obstruction, cannot undergo surgery immediately, or in those whose symptoms cannot be relieved by surgery (evidence quality: B; recommendation strength: weak).

Evidence summary: The guideline development working group conducted qualitative and quantitative research and reviewed nine articles (n = 1013), including five descriptive studies (n = 687), three retrospective cohort studies (n = 268), and one case-control study (n = 58).

The working group conducted a systematic review involving four articles (three retrospective cohort studies and one case-control study, n = 394).[38, 151–153] Three studies (n = 202) compared distal tumor spread in patients with JORRP who underwent tracheostomy and those who did not,[151–153] and found that the rate of lower airway spread of tumors in patients who underwent tracheostomy was higher (RR = 4.33; 95% CI: 2.03, 9.23; P = 0.0002). Another study[38] compared the history of tracheostomy in patients with and without lung involvement (n = 192) and showed that the rate of previous tracheostomy was higher in patients with lung involvement (RR = 0.20; 95% CI: 0.14, 0.28; $P < 0.001$), suggesting that tracheostomy may accelerate the spread of tumors to the lower airway.

The working group conducted qualitative research involving seven articles (one retrospective cohort study, one case-control study, and five descriptive studies, n = 909)[38, 151, 152, 154–157] and extracted data on the patients with JORRP who had distal tumor spread after tracheostomy. The results showed that the rate of intratracheal spread after surgery was significantly higher in patients who underwent tracheostomy than in those who did not (χ^2 = 98.388; $P < 0.001$). In addition, prolonged tracheostomy tube placement correlated with an increased rate of tumor spread to the lower airways. In one retrospective cohort study, 81% (17/21) of patients who underwent tracheostomy and had the tube placed for a long duration exhibited an increased rate of lower airway spread.[151]

A descriptive study reported that of 32 tracheostomies performed in 31 patients with JORRP, no tracheal tumor was seen in the three cases in which the tracheal cannula was removed within 1 month after tracheostomy, while in the remaining 29 cases, varying degrees of papillomatosis growth was observed in the trachea (29/32, 90.6%).[157] This suggests that the prompt removal of the tracheal cannula after tracheostomy is crucial to prevent tumor spread. Four articles (n = 614) highlighted the reasons for performing tracheostomy,[153, 155, 156, 158] including one retrospective cohort analysis (n = 18) and three descriptive studies (n = 596). The findings revealed that among 91 patients who underwent tracheostomy, 32 (35.16%) had grade II or higher laryngeal obstruction at the time of tracheostomy, while 12 (13.18%) had laryngeal obstruction with unclear grade. In addition to laryngeal obstruction, patients who underwent tracheostomy often had other reasons, such as a large surgical wound, heavy bleeding, tissue edema, need for preventive opening (9/44, 20.45%), frequent recurrence (surgery interval of 1–2 months), and no relief despite multiple surgeries (9/44, 20.45%). Economic factors, remote areas of residence, and other factors lead to difficulty in follow-up or inability to undergo immediate surgery (21/44, 47.72%).

Justification: The indications for tracheostomy in patients with JORRP and the timing of extubation after surgery remain controversial. The 2020 IPOG expert consensus also states that tracheostomy is one of the earliest described interventions for RRP and that tracheostomy may still be needed for patients with RRP and lower airway spread or obstructive disease.[9] However, tracheostomy may promote the distal spread of RRP lesions, and its use remains controversial. Based on the evidence in the literature and the opinions of the experts in the guideline development group, the following additional opinions are proposed:

(1) Minimize tracheostomy in patients with JORRP, with strict criteria for its indications, reserving it for specific situations (such as patients with JORRP with symptoms of laryngeal obstruction that cannot be relieved immediately or symptoms that cannot be relieved post-surgery);

(2) Promptly remove tracheostomy tube in patients with JORRP who have undergone tracheostomy, taking into account medical and disease conditions, as well as age;

(3) Tube removal should occur post-stabilization and evaluation ruling out recurrence;

(4) For patients with untreatable tumors involving the lower airway, bevacizumab can be used to control the condition and avoid tracheostomy.

Clinical question 11: What is the optimal timing and frequency for postoperative follow-up for patients with JORRP?

Recommendations: It is recommended that patients seek medical attention immediately after laryngeal obstruction occurs, and timely medical evaluation should be sought when respiratory symptoms such as hoarseness, rough breathing, and snoring occur (GPS).

It is recommended that patients undergo regular follow-ups, and the follow-up frequency be determined individually based on specific patient factors, such as age, HPV genotyping, and number of previous surgeries in clinical practice (GPS).

Evidence summary: Following the literature search, the working group reviewed five descriptive studies ($n = 174$).[159–163] These articles only presented authors' opinions or single-center viewpoints based on clinical experience regarding postoperative follow-up of JORRP. They emphasized the necessity for strict regular follow-ups of patients with JORRP. For instance, one article proposed regular follow-ups every 6 months, while another suggested follow-ups every 3 months for the initial 3 years post-surgery, with weekly follow-ups for the first 5 weeks if the lesion involves the anterior and posterior joints. Another study highlighted the importance of postoperative follow-up, particularly within the first year after surgery, with a focus on the initial 6 months. The remaining studies lacked high-quality evidence to support their recommendations.

The working group designed a Delphi questionnaire and distributed it to experts in the guideline development group, and a total of 21 questionnaires were returned. The results showed that concerning the timing of outpatient follow-up after surgery, 70% of experts chose to follow up in the outpatient department when symptoms of laryngeal obstruction occurred, while 65% chose to follow up in the outpatient department when hoarseness occurred. Notably, 65% of experts chose to follow up at a fixed time frame even in the absence of respiratory symptoms, while 55% of experts chose to follow up in the outpatient department when respiratory symptoms such as noisy breathing and snoring occurred. Regarding the frequency of follow-up, 75% of experts chose to formulate plans according to the patient factors, such as age, HPV typing, and number of previous surgeries, while 55% chose to do outpatient follow-up 1 month after surgery. Furthermore, 45% of experts chose to follow up in the outpatient department 3 months after surgery, 30% chose to follow up in the outpatient department 2 weeks after surgery, and 25% of experts chose not to follow up at a fixed time frame.

Justification: At present, there are different opinions in the literature regarding the timing and frequency of follow-up both locally and abroad, and all are based on the authors' perspectives or single-center experiences. There is still a lack of high-quality research evidence to support such recommendations. Our recommendation is largely based on expert opinions obtained from the Delphi questionnaire. The questionnaire consisted of two questions regarding the timing of outpatient follow-up after JORRP surgery and the follow-up frequency. The questionnaire was distributed to senior otolaryngologists at 15 tertiary hospitals, and the questionnaire return rate was 100%. Experts suggest that patients should seek medical attention immediately when laryngeal obstruction occurs and seek medical evaluation in a timely manner when respiratory symptoms such as hoarseness, noisy breathing, and snoring occur. Furthermore, it is recommended that patients undergo regular follow-ups, and the follow-up frequency can be determined individually based on the specific situation of the patient (e.g., age, HPV typing, number of previous surgeries, etc.).

Clinical question 12: What are the indications, effectiveness, and safety profile of bevacizumab as an adjunct treatment for JORRP?

Recommendations: For patients with rapid disease progression, frequent surgical interventions, and lower airway spread, bevacizumab can be considered an adjunctive treatment (evidence quality: D; recommendation strength: weak).

Evidence summary: The guidelines working group reviewed five articles, including one expert consensus review and four systematic reviews evaluating bevacizumab as an adjunctive therapy for patients with JORRP.

Bevacizumab for RRP can be administered either by intravenous infusion or local infiltration into the tumor. The 2021 International Expert Consensus mainly focused on the systemic application of bevacizumab in the treatment of JORRP.[164] The consensus reached on the indications included a high frequency of surgery, lesions involving the lower airways, extra laryngeal spread, rapid progression, inability to excise lesions during surgery, frequent respiratory distress, and emergency rescue.

Two systematic reviews have described the indications, effectiveness, and safety of the systemic application of bevacizumab in the treatment of RRP. A 2021 systematic review,[165] comprising 12 studies ($n = 20$), including case reports and retrospective case series reports (AMSTAR2 = 9), and another 2022 systematic review[166] of 15 studies ($n = 34$), also including case reports or retrospective case series reports (AMSTAR2 = 5) both included patients with JORRP who needed frequent surgery (80%), and

patients had extra laryngeal lesions (83%). Regarding effectiveness, all patients had improved clinical symptoms, longer intervals between surgery, or a reduced number of surgical interventions post-bevacizumab administration. Furthermore, the 2021 systematic review reported that the effect was maintained well with a follow-up of 2 months–5 years. Concerning safety, both reviews reported Common Terminology Criteria for Adverse Events grade 1–2 side effects during treatment. Proteinuria, hypertension, mild hemoptysis, and acne, with adverse reaction rates of 30% and 29%, respectively, were noted in patients receiving bevacizumab.

A 2022 systematic review[167] involving three retrospective case series studies ($n = 21$, AMSTAR2 = 11) investigated the effectiveness and safety of local application of bevacizumab. After intratumoral injection of bevacizumab, 19 patients (19/21, 90%) exhibited a decrease in Derkay's scores, and 13 patients (13/21, 62%) had fewer surgeries post-medication. In terms of safety, all patients reported no adverse drug reactions.

Regarding the selection of therapeutic modalities for bevacizumab adjuvant therapy for JORRP, a 2022 systematic review[168] (15 studies, $n = 64$, all case reports or retrospective case series studies, AMSTAR2 = 9) described the indications, effectiveness, and safety of systemic and local bevacizumab in the treatment of RRP. The study included 54 patients who underwent JORRP treatment.

Indications: Of the 33 patients who received systemic bevacizumab, 23 (70%) had extra laryngeal lesions, whereas the location of the lesion was not reported in 21 patients who received local bevacizumab.

Effectiveness: All patients experienced longer intervals between surgeries or fewer surgeries after systemic use, whereas only 13 (13/21, 62%) experienced longer intervals between surgeries after local use.

Safety: During systemic use, 13 patients (13/33, 39%) experienced mild side effects, such as proteinuria, nosebleeds, hemoptysis, hypertension, elevated creatinine levels, headaches, thrombocytopenia, hyperthyroidism, taste disorders, nausea, and premature menopause, and no adverse reactions were reported during local injection. The study did not statistically compare the two groups and provided only descriptive data. Considering that the local application of bevacizumab requires general anesthesia and that there is currently a lack of research into the long-term efficacy and adverse effect profile for both routes of administration, the systemic use of bevacizumab can be chosen as the first option. Bevacizumab is administered systemically by intravenous injection; however, the specific dosage is not consistent in current clinical studies. The initial dose is often 5–10 mg/kg, and the initial injection interval is personalized based on the patient's condition.

Justification: Based on the evidence obtained and the 2021 International Expert Consensus, bevacizumab can be considered an adjunctive treatment for patients with rapid disease progression, frequent surgical interventions, and lower airway dissemination. Long-term safety and efficacy data are unclear, and future studies are recommended to focus on this clinical issue in order to provide stronger and more comprehensive evidence. Currently, bevacizumab treatment for JORRP is off-label; therefore, before applying the drug, approval from the ethics committee of the institution must be obtained, as well as informed consent from the patient and their guardians. In addition, the guideline development expert group proposes bevacizumab be administered as an adjunct treatment for JORRP in specific tertiary hospitals. These institutions should have an otolaryngology team with experience in treating JORRP and availability of multidisciplinary diagnostic and treatment teams, consisting of specialists in pediatrics, oncology, respiratory medicine, anesthesiology, pathology, radiology, and intensive care. Simultaneously, participating institutions should strictly control the indications for the use of bevacizumab, have clinical experience in using bevacizumab to treat tumors, and assess and handle complications or adverse reactions in a timely manner.

GUIDELINE DEVELOPMENT PROCESS AND METHODS

Methodology of guideline development, registration, and establishment of the working group

This guideline is based on the methodology for the construction of clinical practice guidelines, in line with the concept of the Institution of Medicine (IOM),[169] and refers to the formulation process and related methodological standards of the "World Health Organization Guideline Development Handbook" released in 2015[170] for the formulation of this guideline. Prior to guideline development, registration was completed on the International Practice Guidelines Registry Platform (http://guidelines-registry.cn/) (registration number PREPARE-2022CN652). In September 2022, a guideline working group was established with four subgroups: guideline steering group, guideline development working group, guideline secretariat, and guideline external review group. These groups were responsible for the supervision and audit of the guideline development process, determination of the guideline scope and clinical issues, consensus on recommendations, drafting and revision of the full text, collection, and selection of clinical issues and outcome indicators for the guidelines, synthesis, and evaluation of evidence, coordination and recording of the formulation process, and review

of the formed guideline recommendations. The clinical experts are primarily concentrated in the key departments responsible for the diagnosis and treatment of this disease, with collaboration from other relevant specialties involved in the therapeutic and perioperative management. These include departments such as Otorhinolaryngology-Head and Neck Surgery, Respiratory Medicine, and Anesthesiology. Notably, approximately 74% of the experts are specialists in otorhinolaryngology-head and neck surgery. The values and wishes of the patients and guardians were considered in the selection of outcome indicators and recommendations.

Methodological support and guidance for this guideline were provided by the Center for Clinical Epidemiology and Evidence-Based Medicine at Beijing Children's Hospital, Capital Medical University.

Collection and selection of clinical questions and outcomes

The evidence synthesis and evaluation subgroup searched for published expert consensus and systematic reviews related to JORRP and conducted one-on-one interviews with otolaryngology clinicians at all levels. The results were categorized, deduplicated, and merged to formulate clinical questions and outcome indicators related to the guidelines. Two rounds of Delphi surveys were conducted, and a consensus meeting, combining online and offline surveys, was held. After multiple discussions by the guideline development working group, the final 12 clinical questions of concern were determined, including four diagnostic-related questions and eight treatment-related questions. Clinical questions were constructed based on the PICO (Population, Intervention, Comparison, Outcome) principles. At the same time, the list of outcome indicators was drawn up through literature inquiry and in-depth interviews, and after many discussions in the guideline formulation working group, four effectiveness indicators and one safety indicator were finally determined.

Search, synthesis, and evaluation of evidence

During the stages of theme and scope determination, evidence synthesis, and evaluation, this guideline development working group carried out a search and evaluation of RRP (including JORRP + AORRP)-related guidelines, expert consensus, and systematic reviews/meta-analysis. When answering the clinical questions, the corresponding original research was searched, and a qualitative/quantitative systematic evaluation was conducted.

Inclusion and exclusion criteria

Inclusion criteria:

1. Participants: Children diagnosed with JORRP, with the age of first onset at 0–18 years;
2. Intervention and comparison measures: Only bevacizumab-related interventions are included in drug interventions, other measures are not limited;
3. Outcomes: Not limited;
4. Study types: Clinical guidelines, expert consensus, systematic reviews, Meta-analyses, relevant clinical research, and some basic research (limited questions are included).

Exclusion criteria:

Literature that only included AORRP patients, nursing-related literature, literature with intervention and comparison measures such as traditional Chinese medicine (herbal medicine, prepared Chinese medicine, acupuncture, etc.), and duplicate publications and proposals were excluded.

Data sources and search strategies

Data sources include: English database searches, including PubMed, Embase, The Cochrane Library, and Web of Science, and the search time was from the inception of the library to August 2023. Chinese databases, such as CBM, CNKI, VIP, and WanFang Data were explored. The search period was from inception to May 2023. The main search terms were different expression modes of recurrent respiratory papillomatosis. Among them, PubMed searches RRP-related literature mainly for disease search terms. Recurrent Respiratory Papillomatosis, Laryngeal Papillomatosis, Respiratory Papillomatosis, JORRP, According to the requirements of different databases, we use a combination of subject terms and free terms to search.

Evidence screening and data extraction

Literature screening: At least two evaluators in a group independently performed literature screening based on the inclusion and exclusion criteria. Irrelevant literature was excluded by reading the title and abstract, and the full text of the remaining literature was read to determine the literature that met the inclusion and exclusion criteria. The literature screened by the two evaluators has a duplication rate of ≥85%, which is considered to be qualified for screening. Data extraction stage: A personalized data extraction form was prepared, and at least two evaluators extracted relevant data from the included literature. Disagreements were resolved through group discussions or consultations with a third party.

Evidence evaluation

The AMSTAR2 tool was used to evaluate the methodological quality of the included systematic reviews.[171] If

the study is a high-quality systematic review and/or meta-analysis, it can be used directly. If the time from publication is more than 2 years, it will be updated. Some clinical questions currently lack published systematic reviews and/or meta-analyses, and the Guideline Development Working Group has reformulated the related systematic reviews and meta-analyses. The Newcastle-Ottawa scale was used to evaluate the methodological quality of the included cohort and case-control studies, while the Quality Assessment of Diagnostic Accuracy Studies 2 was used to evaluate the methodological quality of the included diagnostic trials. Furthermore, The Cochrane bias risk assessment tool (risk of bias, ROB) was used to evaluate the ROB of the included RCTs, and it was completed independently by two people. Any inconsistency was resolved through discussion or consultation with a third party.

These guidelines use GRADE to grade the evidence for each clinical question (Table 2). The quality of evidence is divided into four levels: high, medium, low, and very low, and the strength of recommendation is divided into strong and weak (http://www.gradeworkinggroup.org/). The GRADE evidence quality grading process considers five downgrade factors: ROB, consistency, precision, publication bias, and indirectness, and three upgrade factors: large effect size, confounding bias, and dose response. The level of evidence is presented through evidence summary tables.

Formulation of recommendations

The guideline development working group formulated 37 recommendations to seek expert advice based on the evidence of international systematic reviews related to each clinical question and the systematic review evidence formulated by the guideline development working group. They also considered the balance of benefits and costs of intervention measures while formulating interventions. Through two rounds of Delphi questionnaire surveys and a face-to-face expert consensus meeting held in Zhuhai, Guangdong Province, on November 3, 2023, 203 feedback opinions were collected. The working group discussed and approved all recommendations and evidence quality, modified and merged the recommendations, and the consensus degree ≥80% was regarded as consensus adoption and finally formed 24 recommendations.

Draft an external review of the guidelines

The draft of the guidelines was reviewed by six external peer experts and was improved based on their suggestions. Finally, the guideline development group submitted the guidelines to the steering group for approval.

DISSEMINATION AND IMPLEMENTATION

After the publication of this guideline, the guideline-initiating unit disseminates it through academic conference reports, lectures across the country, WeChat public accounts, and so on.

Estimation of favorable and unfavorable factors in guideline implementation Favorable factors: Improve the diagnostic accuracy of the disease, deepen the understanding and planning of JORRP treatment, and reduce the prevalence of disease recurrence and adverse reactions. Unfavorable factors: 1.) This guideline includes the use of cold instruments, CO_2 lasers, and low-temperature plasma knives for the treatment of JORRP in clinical questions, and intends to compare their safety and effectiveness, but no corresponding evidence for the evaluation of low-temperature plasma knife treatment was obtained during the literature collection process. Regarding the effectiveness and safety of bevacizumab in the treatment of JORRP, although an international expert consensus was published in 2021, there is still a lack of high-quality evidence and long-term follow-up data. Therefore, strict criteria for indications are required when utilizing bevacizumab clinically, and caution should be exercised to avoid harming the interests of children.

UPDATE OF THE GUIDELINE

The preparation team plans to update this guideline 3–5 years after their publication. The updated method will be based on an international guideline update process.

VERSION STATEMENT

There are two versions of this guide, Chinese and English. The Chinese version will be published by the *Chinese Journal of Otorhinolaryngology-Head and Neck Surgery*, and the English version will be jointly published by *Pediatric Investigation* and the *World Journal of Otorhinolaryngology-Head and Neck Surgery*. The supporting data of the guideline are stored in the National Center for Children's Health/Beijing Children's Hospital affiliated with Capital Medical University.

LIST OF EXPERTS

See supporting File S1.

CONFLICT OF INTEREST

All participants involved in the formulation of the guidelines declare no financial or nonfinancial conflicts of interest directly related to these guidelines. The guide is

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